Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 18-63 under 35 U.S.C. §112, second paragraph, because of the phrases, "LDCAM polypeptide" and "B7-L1 polypeptide," which, as the Examiner alleged, are arbitrarily named and thus do not establish the metes and bounds thereof.

Applicants respectfully traverse this rejection and submit that these phrases are not indefinite as they are clearly described in the instant specification. With respect to "LDCAM polypeptide," Applicants refer the Examiner to page 5, first full paragraph, where LDCAM is described as to which polypeptides the term encompasses. With respect to "B7L-1 polypeptide", Applicants refer the Examiner to the sentence bridging pages 2 and 3, where B7L-1 is referred to as described in a related application, S/N 60/095,663, filed August 7, 1998, the non-provisional application of which is now U.S. Pat. No. 6,512,095. For the Examiner's convenience, a copy of the '095 is enclosed herewith; the Examiner is referred to the first full paragraph of column 2 of this patent where B7L-1 is described.

The Examiner rejected claims 35, 36 and 46-54 under 35 U.S.C. §112, second paragraph, because the language for the hybridization conditions as recited, "moderate stringency" or "severe stringency," renders the claims to be "ambiguous." The Examiner also alleged that there does not appear to be a definition in the specification as filed that clearly provides the metes and bounds of these conditions.

Applicants respectfully traverse this rejection and submit that the claims are not indefinite as the Examiner alleged. The specification as filed describes the conditions for both "moderate stringency" and "severe stringency." The Examiner is referred to the paragraph that bridges pages 9 and 10 of the specification, where the conditions as claimed are described in details.

In view of Applicants' traversal to the rejection made under 35 U.S.C. §112, second paragraph, as presented in the foregoing paragraphs, Applicants respectfully request the Examiner to withdraw this rejection.

Rejection under 35 U.S.C. §112, first paragraph (non-enablement)

The Examiner rejected claims 18-63 under 35 U.S.C. §112, first paragraph, because, as the Examiner alleged, the specification does not enable for polypeptides

(a) that comprise a sequence of at least 80% or 90% identical to SEQ ID NO: 2 or 4; (b) that bind to any LDCAM or B7L-1; (c) that comprise fragments other than the extracellular domain; or (d) that comprise amino acid variance of unlimited number of insertions, deletions, or substitution. With respect to (a), the Examiner suggested the claims to be limited to polypeptides that have a 95% identity to the full length (of SEQ ID NO: 2 or SEQ ID NO: 4) and binding activity. Office Action, page 4, second paragraph.

Applicants respectfully submit that the claims are enabled because they can be practiced without "undue experimentation." *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The key word here is "undue," not "experimentation," as reiterated in *Wands* from *In re Angstadt* (190 USPQ 214 (C.C.P.A. 1976)). According to *Wands*, "whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Wands* went on to reiterate the factors that must be considered in determining undue experimentation as summarized in *Ex parte Forman* (230 USPQ 547). These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims. Based on this guidance, Applicants respectfully point out that the Examiner has not provided an adequate basis when making this rejection. This deficiency not withstanding, Applicants submit why Applicants clearly satisfy the standard for enablement as articulated in *Wands*, as follows.

With respect to the amino acid sequence limitation, Applicants teach a wide variety of variants that include polypeptides that are at least 80% or 90% identical to SEQ ID NO: 2 or SEQ ID NO: 4, to variants that comprise conservative amino acid substitutions, to fusion polypeptides comprising LDCAM. For example, see pages 5-8, in particular the paragraph bridging pages 5 and 6:

> A "LDCAM variant" as referred to herein, means a polypeptide substantially homologous to native LDCAM, but which has an amino acid sequence different from that of native LDCAM (human, murine or other mammalian species) because of one or more deletions, insertions or substitutions. The variant amino acid sequence preferably is at least 80% identical to a native LDCAM amino acid sequence, most preferably

> at least 90% identical. The percent identity may be determined, for example, by comparing sequence information using the GAP computer program, version 6.0 described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) for nucleotides, and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745, 1986, as described by Schwartz and Dayhoff, eds., *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps. Variants may comprise conservatively substituted sequences, meaning that a given amino acid residue is replaced by a residue having similar physiochemical characteristics. Examples of conservative substitutions include substitution of one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp; or Gln and Asn. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobicity characteristics, are well known. Naturally occurring LDCAM variants or alleles are also encompassed by the invention. Examples of such variants are proteins that result from alternate mRNA splicing events or from proteolytic cleavage of the LDCAM protein, wherein the LDCAM binding property is retained. Alternate splicing of mRNA may yield a truncated but biologically active LDCAM protein, such as a naturally occurring soluble form of the protein, for example. Variations attributable to proteolysis include, for example, differences in the N- or C-termini upon expression in different types of host cells, due to proteolytic removal of one or more terminal amino acids from the LDCAM protein (generally from 1-5 terminal amino acids). (emphasis added)

Applicants also teach a variety ways of how to make these amino acid substitutions, for example, oligonucleotide-directed mutagenesis (page 10, lines 11-18).

With respect to the biological activity of the claimed polypeptides, Applicants also teach how to determine whether they are capable of binding a LDCAM polypeptide or B7L-1 polypeptide or both, the functional limitation in the claims. See pages 10-12, in particular, page 10, lines 30-37, page 11, lines 1-8; Examples 2 and 5.

> Variants possessing the ability to bind B7L-1 may be identified by any suitable assay. Biological activity of LDCAM may be determined, for example, by competition for binding to the binding domain of B7L-1 (i.e. competitive binding assays).
>
> One type of a competitive binding assay for a LDCAM polypeptide uses a radiolabeled, soluble LDCAM and intact cells expressing B7L-1-expressing. Instead of intact cells, one could substitute soluble B7L-1/Fc fusion proteins such as a B7L-1/Fc bound to a solid phase through the interaction of a Protein A, Protein G or an antibody to the B7L-1 or Fc portions of the molecule, with the Fc region of the fusion protein.

> Another type of competitive binding assay utilizes a radiolabeled soluble LDCAM receptor and intact cells expressing LDCAM.
>
> Competitive binding assays can be performed following conventional methodology. For example, radiolabeled LDCAM can be used to compete with a putative LDCAM homologue to assay for binding activity against B7L-1 or a surface-bound LDCAM receptor. Qualitative results can be obtained by competitive autoradiographic plate binding assays, or Scatchard plots may be utilized to generate quantitative results. (emphasis added)

Thus one skilled in the art, guided by Applicants' disclosure, can make the polypeptides as claimed. Consequently, the claims satisfy the Federal Circuit's standard for enablement. Accordingly Applicants respectfully request that the rejection be withdrawn.

With respect to the Examiner's cited publications in support for the non-enablement position – Atwood, Skolnick et al., and Metzler et al. – Applicants submit that their teachings are not applicable in the context of the instantly claimed invention. While the former two publications discuss the unreliability of deducing structure and function of protein for an unknown gene based on sequence homology to genes of known functions, the instantly claimed LDCAM is a functionally known protein, and for this matter a known gene, as discovered by Applicants and described in the instant application. The polypeptides as instantly claimed are limited to those that are capable of binding to LDCAM and/or B7L-1; they are not proteins for which functions are not known as discussed in these publications. Similarly, while Metzler et al. teaches that an amino acid mutation can abolish an enzyme activity, its teaching is not applicable in the context of the instantly claimed invention. This is because the instantly claimed polypeptides are limited to those that are capable of binding to LDCAM and/or B7L-1. Polypeptides, mutated or not, that are not capable of binding LDCAM and/or B7L-1 will therefore are not encompassed in the scope of the invention.

Regarding *Colbert v. Lofdahl*, 21 USPQ2d, 1068, 1071 (BPAI 1992), which is cited by the Examiner to support the position that the language "LDCAM" and "B7L-1" would mean "any" LDCAM or B7L-1 polypeptides whose structural information is not sufficiently provided. As stated in the response to the 112/2 rejection above, Applicants refer the Examiner to page 5, first full paragraph, where LDCAM is described as to which polypeptides it encompasses. With respect to "B7L-1 polypeptide", Applicants refer the Examiner to the sentence bridging pages 2 and 3, where B7L-1 is referred to

as described in a related application, S/N 60/095,663, filed August 7, 1998, the non-provisional application of which is now U.S. Pat. No. 6,512,095. Applicants thus submit that the structure for LDCAM and B7L-1 are sufficiently provided. Applicants also submit that *Colbert* is not applicable to the instant case, as the facts in *Colbert* and the instant case are not the same. While *Colbert* relates to the issue of conception of the invention, the isolation of a new gene, in the instant case, the nucleic acid encoding LDCAM, and its polypeptide, are already isolated by Applicants.

In view of Applicants' traversal to the rejection made under 35 U.S.C. §112, first paragraph, as presented in the foregoing paragraphs, Applicants respectfully request the Examiner to withdraw this rejection.

Rejection under 35 U.S.C. §102(e)

The Examiner rejected claims 18-63 under 35 U.S.C. §102(e) as being anticipated by Baker et al. (U.S. 2002/0198147). In response to this rejection, Applicants submit herewith a Rule 131 Declaration signed by all the inventors. The declarants describe the nucleic acid and amino acid sequence of human LDCAM prior to December 03, 1997, the earliest possible 102(e) date of the cited patent application publication. Accordingly, Applicants submit that they have broadly established a completion of an embodiment of the invention prior to the date of the cited art.

In view of Applicants' 131 Declaration, Applicants respectfully request the Examiner to withdraw this rejection.

Conclusion

In view of the foregoing remarks, Applicants respectfully request that a timely Notice of Allowance be issued for this case.

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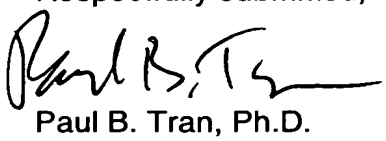
Respectfully submitted,



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